16. Lavin Y, Kobayashi S, Leader A, Amir ED, Elefant N, Bigenwald C, *et al.* Innate immune landscape in early lung adenocarcinoma by paired single-cell analyses. *Cell* 2017;169:750–765.e17.
17. Yanagawa J, Tran LM, Fung E, Wallace WD, Prosper AE, Fishbein GA, *et al.* Single-cell characterization of subsolid and solid lesions in the lung adenocarcinoma spectrum [preprint]. *bioRxiv*; 2020 [accessed 2021 Aug 27]. Available from: https://www.biorxiv.org/content/10.1101/2020.12.25.424416v1.

Intermittent Hypoxemia and Bronchopulmonary Dysplasia: Manifestations of Immature Respiratory Control and the Preterm Lung

Bronchopulmonary dysplasia (BPD), first reported by Northway and colleagues (1), continues to be redefined in its diagnosis, causalities, and therapies (2). BPD is a heterogeneous chronic condition of parenchymal, airway, and cardiovascular pathology after preterm birth that has strong associations with adverse childhood morbidities (3). It is a disease both caused by and defined by the degree of respiratory therapy needed to prevent hypoxemia and death during the first weeks of life. New data indicate that unfavorable responses to these therapies, as measured by an increase in intermittent hypoxemic events, may contribute to or are associated with the diagnosis of severe BPD at 36 weeks' postmenstrual age (4).

Intermittent hypoxemia (IH) is an emerging descriptor of the physiologic manifestations of immature respiratory control and the developmentally preterm lung. In this issue of the *Journal*, Jensen and colleagues (pp. 1192–1199) describe, in a multinational cohort of more than 1,000 preterm newborns, associations in the first weeks of life between both prolonged IH events (oxygen saturation [Sp_{O_2}] $<$ 80% for $>$1 min as measured by pulse oximetry) and cumulative hypoxemia (% time with $Sp_{O_2} <$ 80%) with future diagnosis of severe BPD (4). This work confirms reported associations between IH and BPD from smaller single-center cohorts (5, 6) and that IH events in extremely preterm newborns increase in frequency during the first weeks of life, even in newborns in whom BPD was not diagnosed. Furthermore, this study confirms associations between severe BPD and late death or adverse neurodevelopment suggesting that early and prolonged IH may contribute to the known risk of poor developmental outcomes in infants with severe BPD.

A range of IH definition criteria have been described in the neonatal research literature including a fall in Sp_{O_2} to $<$80–85% with or without accompanying duration criteria. Is a threshold of $<$80%, as used by Jensen and colleagues and others, too low considering American Academy of Pediatrics recommendations for Sp_{O_2} targets of 90–95% (4)? Or appropriate to reduce supplemental oxygen exposure? The jury is still out. Minimum duration criteria are also important in identifying "shorter" events that do not require intervention. Jensen and colleagues report on IH $>$1 minute in duration based on their previous data showing that shorter IH events were not associated with poor outcomes in this cohort (7). Previous single-site studies have confirmed an association between longer IH duration and BPD, although neither study identified a specific duration cutoff (5, 6). The authors did not report a maximum duration threshold, which is important to distinguish intermittent from sustained hypoxemia that can have differing physiological effects (8). Lastly, Raffay and colleagues looked at the time interval between subsequent IH events and found that BPD infants had more event clusters occurring $<$1 minute and 1–20 minutes apart with no differences observed in isolated events ($>$20 min apart) (6). Taken as a whole, these studies suggest that not all IH events may be detrimental and future trials should focus on identifying high risk patterns of IH.

An important contributor that can influence identification of high-risk patterns is the pulse oximeter averaging time. With no current standard, 8 or 10 seconds is the most commonly used setting in the neonatal ICU to reduce nuisance alarms. Longer averaging times can result in short, closely clustered IH being combined into fewer but longer events (9). Thus, with the 16-second averaging time used by Jensen and colleagues, interpretation of IH $<$1 minute in duration as nonhazardous should be made with caution.

Pulse oximetry may be an important noninvasive tool that can identify infants at risk for poor outcomes. Jensen and colleagues note that IH frequency, more so than time spent in hypoxemia, predicted BPD risk, suggesting current-generation oximeter Sp_{O_2} histograms could be improved. More sophisticated unbiased modeling of large data sets could give insight into which IH parameters are important. One such effort to investigate the entire Sp_{O_2} waveform is the Pre-Vent multicenter trial of more than 500 extremely preterm patients from five contributing centers (10). Investigators will use the highly comparative time-series analysis developed by Fulcher and colleagues (11) to identify a range of models that best describe the longitudinal profile of cardiorespiratory waveform patterns during the first few months of life. The goals of this collaborative are to delineate mechanisms of immature ventilatory control in preterm infants and to identify predictive markers and ascertain their contributions to respiratory morbidities, including but not limited to traditional BPD definitions as extremely preterm newborns are likely to display some

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BPD phenotype in terms of lung development and longer-term outcomes (2). The results from this trial could inform the next generation of advanced pulse oximeter monitoring.

Complicating interpretation of observational IH data is the concomitant use of supplemental oxygen to treat hypoxemia and maintain Sp_{O_2} targets. Of note, higher Sp_{O_2} targets are associated with decreased IH events (12) but also increased supplemental oxygen use at 36 weeks' postmenstrual age (13). As noted by the authors, determining association versus causation from observational studies and confounding by indication remains a challenge. What can reasonably be speculated is that the most at-risk infants for BPD likely have the worst respiratory control, worst lung disease, and most IH events and are on the highest $F_{I_{O_2}}$. Looking to translational animal studies (14, 15) exposure to intermittent hypoxia alone does not result in a BPD phenotype; however, when superimposed with hyperoxia, the lung pathology occurs in excess of sustained hyperoxia alone. Thus, the hyperoxic overshoot after an IH event may be the villain to battle.

Classifying pathologic versus expected patterns of IH will be critical to understanding and predicting risk for poor respiratory outcomes, particularly as automated supplemental oxygen titration enters the clinical realm (16, 17). ■

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References

1. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357–368.
2. Jobe AH, Bancalari E. An all-inclusive perspective on bronchopulmonary dysplasia. *J Pediatr* 2021;234:257–259.
3. Collaco JM, McGrath-Morrow SA. Respiratory phenotypes for preterm infants, children, and adults: bronchopulmonary dysplasia and more. *Ann Am Thorac Soc* 2018;15:530–538.
4. Jensen EA, Whyte RK, Schmidt B, Bassler D, Vain NE, Roberts RS; Canadian Oxygen Trial Investigators. Association between intermittent hypoxemia and severe bronchopulmonary dysplasia in preterm infants. *Am J Respir Crit Care Med* 2021;204:1192–1199.
5. Fairchild KD, Nagraj VP, Sullivan BA, Moorman JR, Lake DE. Oxygen desaturations in the early neonatal period predict development of bronchopulmonary dysplasia. *Pediatr Res* 2019;85:987–993.
6. Raffay TM, Dylag AM, Sattar A, Abu Jawdeh EG, Cao S, Pax BM, *et al.* Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age. *Pediatr Res* 2019;85:318–323.
7. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, *et al.*; Canadian Oxygen Trial Investigators. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *JAMA* 2015;314:595–603.
8. Wu W, Dave NB, Yu G, Strollo PJ, Kovkarova-Naumovski E, Ryter SW, *et al.* Network analysis of temporal effects of intermittent and sustained hypoxia on rat lungs. *Physiol Genomics* 2008;36:24–34.
9. McClure C, Jang SY, Fairchild K. Alarms, oxygen saturations, and SpO2 averaging time in the NICU. *J Neonatal Perinatal Med* 2016;9:357–362.
10. Dennery PA, Di Fiore JM, Ambalavanan N, Bancalari E, Carroll JL, Claure N, *et al.* Pre-Vent: the prematurity-related ventilatory control study. *Pediatr Res* 2019;85:769–776.
11. Fulcher BD, Georgieva AE, Redman CW, Jones NS. Highly comparative fetal heart rate analysis. *Annu Int Conf IEEE Eng Med Biol Soc* 2012; 2012:3135–3138.
12. Di Fiore JM, Walsh M, Wrage L, Rich W, Finer N, Carlo WA, *et al.*; SUPPORT Study Group of Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia. *J Pediatr* 2012;161:1047–1052.
13. Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, *et al.*; Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. *JAMA* 2018; 319:2190–2201.
14. Ratner V, Slinko S, Utkina-Sosunova I, Starkov A, Polin RA, Ten VS. Hypoxic stress exacerbates hyperoxia-induced lung injury in a neonatal mouse model of bronchopulmonary dysplasia. *Neonatology* 2009;95: 299–305.
15. Dylag AM, Mayer CA, Raffay TM, Martin RJ, Jafri A, MacFarlane PM. Long-term effects of recurrent intermittent hypoxia and hyperoxia on respiratory system mechanics in neonatal mice. *Pediatr Res* 2017;81:565–571.
16. Hummler H, Fuchs H, Schmid M. Automated adjustments of inspired fraction of oxygen to avoid hypoxemia and hyperoxemia in neonates - a systematic review on clinical studies. *Klin Padiatr* 2014;226:204–210.
17. Claure N, Bancalari E. Targeting arterial oxygen saturation by closed-loop control of inspired oxygen in preterm infants. *Clin Perinatol* 2019; 46:567–577.